REMARKS

With entry of this Amendment, claims 29-50 are pending in the application. By this amendment, claims 23-28 have been cancelled and new claims 29-50 added, for clarity in accordance with the Office's suggestions. The amendments herein are fully supported by the disclosure, and no new matter has been added to the application. The cancellation of claims herein is intended without prejudice to prosecution of any subject matter supported by the disclosure, and is solely presented for clarity to advance certain aspects of the invention to issuance. No subject matter is hereby disclaimed, and the purpose and result of this amendment is not to narrow or otherwise limit the subject matter of the invention in any aspect or manner. Entry of this amendment and reconsideration of the application is respectfully requested.

Patentability Under 35 USC § 112

Applicants acknowledge that the previously-levied rejections under 35 USC § 112, first and second paragraphs, have been reconsidered and withdrawn.

Claims 23-28 are currently rejected under 35 USC § 112, first paragraph for allegedly lacking written descriptive support. While Applicants disagree with the merits of this rejection, the rejection is obviated by cancellation of the claims to which the rejection was originally directed. The stated grounds for this rejection notably do not apply to any of the now-pending claims. Accordingly, it is believed that all issues pertaining to patentability of the invention under 35 USC § 112, first and second paragraphs, have been resolved favorably.

Patentability Under 35 USC § 103

Former claims 23-28 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Keith (WO 83/00286) ("Keith") in view of Kondrat'eva et al. ("Kondrateva") and Joshi et al. (USPN 5,252,318) ("Joshi") and Handbook of Experimental Excipients, 2nd Ed., p. 383 ("Handbook"), further in view of "Remington: The Science and Practice of Pharmacy" (17th ed.), A.R. Gennaro, 1985, pp. 1308 and 1159 ("Remington"), Osol et al. (Remington's Pharmaceutical Sciences, 15th ed., 1975)

("Osol") and "Applicant admission regarding the prior art in the specification (see page 7-8)".

Applicants respectfully traverse the stated grounds for rejection set forth under 35 U.S.C. 103(a) (as summarized above and further presented at pages 5-11 of the Office Action), and submit that the cited references, taken as a whole, fail to disclose or suggest the instantly claimed subject matter of the invention. Although the rejected claims are cancelled herein, the stated grounds for rejection are addressed herein as though applied to the currently-amended claims, without prejudice.

To properly construe these facts of record, the Office's attention is respectfully directed to the long-standing decision of *In re Taborsky* (183, USPQ 50, 55 CCPA, 1974). There, the Federal Circuit's predecessor court clarified the standards for determining obviousness, as follows:

> In determining the propriety of the Patent Office case for prima facie obviousness, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the proposed substitution or other modification.

As similarly set forth in the Manual of Patent Examining Procedure (MPEP § 2143.01):

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

The Office cites Kieth for allegedly teaching a scopolamine formulation that is highly effective for treating motion sickness and nausea. Kieth's scopolamine formulation is a simple aerosol spray made by dissolving scopolamine hydrochloride in a stock solution of 20% alcohol in water (see, e.g., Keith, at page 3, Example I). Keith's allegedly fast-acting and effective formulations represent the "state of the art" for therapeutic scopolamine formulations at the time of the invention.

At the same time, the Office concedes the many shortcomings of Keith: (1) Keith fails to disclose the use of polyvinyl alcohol (PVA) for any purpose in a scopolamine

formulation, alone or with one or more additional gelling agents or bioadhesives; (2) Kieth fails to disclose a desired pH for a scopolamine formulation within the presently-claimed range ; (3) Keith fails to teach a buffer salt concentration for an intranasal scopolamine formulation of less than or equal to about 100 mM or 50 mM, or about 20 mM.

While the Office thus acknowledges the deficiencies of Kieth, Examiner provides no direct suggestion to modify the primary teachings of Keith to incorporate any of the presently claimed features of Applicants' invention, including: the use of PVA; pH range; buffers; modified buffer concentrations; particular scopolamine salts; additional gelling agents/bioadhesives; and preservatives. These shortcomings of Keith are not remedied by any of the five secondary references cited by the Office, taken alone or in combination. Moreover, neither Kieth nor any of the cited secondary references provides evidence of a problem, or proposes specific directions for improvement or "optimization", with regard to Keith's scopolamine formulation. The Office's own analysis supports a conclusion that no specific disadvantages to Kieth's formulations were ever realized that could serve as a coherent basis to develop and apply direction and guidance—at least prior to Applicants' disclosure.

The Office contends that one of ordinary skill in the art would have been motivated "to optimize the pH" of an intranasal scopolamine formulation to below about 4 or 3.5, and "to optimize the concentration of the buffer salt" in such formulation to below about 100 mM or 50 mM. However, Kieth "teaches away" from any need to modify or optimize pH or modify buffer conditions/concentrations. Specifically, Kieth teaches simple, aqueous/alcohol scopolamine formulations interpreted by the Office as being highly effective. In accord with the Office's view, Keith describes these simple formulations as providing "quick action", "sustained relief" and "no side effects". These characterizations are inconsistent with a direct suggestion or motivation to modify Kieth's formulations as the Examiner proposes.

To properly analyze the role of suggestion or motivation in determining obviousness, the Examiner "must consider the problem confronting the applicant in order

to ascertain how a person of ordinary skill would view the problem and its solution." *In re Dillon*, 13 USPQ2d 1337, 1341 (Fed. Cir. 1990). "[D]iscovery of the source of a problem' is part of the 'subject matter as a whole' to be considered in determining obviousness." *Id.*, 13 USPQ2d at 1343 (quoting *In re Sponnable*, 160 USPQ 237, 243 (CCPA 1969).

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made." *In re Gyurik*, 201 USPQ 552, 557 (CCPA 1979).

Notions of general "optimization" are not consistent with express requirements for "practical" motivation--and the record in the instant case fails to elucidate any problems of consequence relating to the Kieth formulation that would lead the artisan to test specific, practical solutions to such problems. As further explained in the case of *In re Shaffer*, 108 USPQ 326, 329 (CCPA 1967):

> [A] person having the references before him who was not cognizant of appellant's disclosure would not be informed that the problems solved by appellant ever existed. Therefore, can it be said that these references which never recognized appellant's problem would have suggested its solution? We think not, and therefore feel that the references were improperly combined since there is no suggestion in either of the references that they can be combined to produce appellant's result.

Even if specific problems or directions for improvement of the Kieth formulation were identified by the Office, the art of record still would not yield substantial motivation to modify the simple aqueous/alcohol scopolamine formulations of Kieth in the numerous, specific, and unrelated ways proposed by the Office. The cited references, taken as a whole, simply fail to disclose or suggest the desirability of Applicants' innovative modifications—whereby the rejection, based on an attenuated combination of primary and secondary teachings, should be dismissed as impermissible hindsight reconstruction of Applicants' invention.

In the instant case, nothing in the record suggests modifying the Keith scopolamine formulations by adjusting the pH to specific values within the ranges set forth in Applicants' claims. Likewise nothing in the record suggests modifying Kieth's formulations by adding specific buffer salts, or by employing buffer salts in specific concentrations as recited in the instant claims. Accordingly, no *prima facie* case of obvious has been made, and the rejection of claims under 35 U.S.C. 103(a) as allegedly unpatentable over Keith in view of the five cited secondary references is believed to be overcome.

The Office contends that one of ordinary skill in the art would have been motivated "to optimize the pH" of an intranasal scopolamine formulation to below about 4 or 3.5 . . . and "to optimize the concentration of the buffer salt" in a scopolamine formulation to below about 200 mM or 100 mM or 50 mM. Again, no documentary evidence or specific, scientific reasoning is provided by the Office in support of these contentions.

Contrary to the Office's position, the primary reference must be interpreted as "teaching away" from any need to modify or optimize the simple, aqueous/alcohol scopolamine formulations reported by Keith—consistent with Office's own interpretation that the formulations of Keith are highly effective for their intended purpose.

With regard to the inclusion of PVA, the Office formerly argued that Kieth describes the use of various "carrier" agents, and that the reference by Osol et al. describes PVA as an alternative "carrier" for substitution within the formulation of Kieth. Applicants responded by noting that Osol et al. specifically define PVA as an "emulsifying and suspending agent"—as distinguished from the generic "carrier" proposed by the Office for substitution in the Kieth formulation. Applicants further noted that the Kieth formulation is limited to a simple alcohol-in-water formulation, whereas Osol specifically teaches the use of emulsifying and suspending agents "to overcome agglomeration of the dispersed particles, and to increase the viscosity of the medium . . ."

Thus, even if Keith suggested a generic utility for alternative "carriers", the use for PVA provided by Osol, as an "emulsifying and suspending agent", is contrary to the

purpose of a "carrier" as described by Kieth. In particular, Keith teaches addition of a viscosity-lowering excipient to water to enhance scopolamine delivery in an intranasal formulation. The artisan would therefore be led away from the path suggested by Examiner.

Examiner cites Kondrat'eva to support the proposed substitution of PVA in a scopolamine formulation as allegedly described in Kieth. However Kondrat'eva's formulation, directed to an ophthalmic (eye drop) solution, uses PVA as a substitute "carrier" not as a stabilizing agent or "viscosity increasing agent" as in Examiner's proposed combination. There is no support in the record to employ PVA as a stabilizing or viscosity increasing agent in Keith's formulation. There is no stability problem reported by Kieth and no suggestion to use PVA for any purpose in a scopolamine formulation outside the limited context of Kondrat'eva, which simply describes the use of PVA to increase the shelf life of ophthalmic solutions. Even if PVA was generally known to be an effective stabilizing agent for pharmaceutical preparations, which is not believed to be the case, there is no direct suggestion to modify the formulation of Kieth for this purpose, much less to employ PVA to achieve this objective. Moreover, if PVA was selected as an agent to enhance stability of the Kieth formulation, this modification would have been expected to increase the viscosity of the formulation. As noted above, Kieth expressly teaches against such modification, because the formulation of Kieth employs a viscosity-lowering excipient (alcohol) to optimize an intranasal scopolamine spray formulation.

In view of the foregoing, the record is clear that Keith in combination with Kondrat'eva fail to teach or suggest the desirability of using PVA in an intranasal scopolamine formulation. It is likewise apparent that Kieth in combination with Kondrat'eva fail to disclose or sufficiently motivate independent development of an intranasal scopolamine formulation comprising PVA in a concentration of about 10% (claims 32 and 43). It is extremely difficult to conceive how such a discrete concentration value range could be suggested among the combined references, particularly considering that Examiner has proposed substituting PVA into the Kieth formulation for five, separate and distinct, hypothetical purposes (i.e., as a "carrier" or to

overcome agglomeration of dispersed particles in view of Osol, as a lubricant per the Office (Office Action at p. 9), or as a stabilizer or to increase viscosity, in view of Kondrat'eva)

To the extent the foregoing facts are deemed by the Office to establish a *prima facie* case of obviousness to support a rejection of claims directed to a combined scopolamine/PVA formulation, it is further submitted that Applicants' disclosure evinces "unexpected results" for the claimed formulations and methods. In this context, Applicants' Examples clearly evince that scopolamine/PVA formulations of the invention are not only more stable than scopolamine formulations using alternative carriers and gelling agents (e.g., methyl cellulose), but their bioavailability is also surprisingly enhanced. It is respectfully submitted that the stability results are not predictable and are therefore unexpected in light of the combined teachings of Kieth and Kondrat'eva, for the reasons stated above. However, even if these data are dismissed, it is clear that Applicants' improved bioavailability data represent unexpected results. Nothing in the art of record suggests the observed bioavailability improvements, and in fact Kieth teaches directly away from employing PVA for this purpose, based on its known activity to increase viscosity and the express teachings by Kieth to use a viscosity lowering agent (alcohol) in intranasal scopolamine formulations.

Further in regard to Applicants' novel pH values and buffering agents/concentrations for their formulations, the Office again presents new lines of reasoning to address these aspects of the invention. In particular, yet another new reference, Joshi, is cited for allegedly teaching "that by adjusting or controlling the pH of these drug delivery systems in an aqueous base through the addition of buffering agents, the viscosities of the compositions or formulations may be various." (emphasis supplied by Examiner).

The Office cites Joshi as a secondary reference directed toward altering pH and buffer values to adjust viscosity of gelling formulations. Joshi does not cure the deficiencies of Keith. First, Kieth makes no mention of viscosity adjustment using pH or buffer agents/values. On the contrary, Kieth uses a viscosity lowering excipient (alcohol)

to provide a reportedly highly successful intranasal scopolamine formulation, as affirmed by the Office. To improve this formulation by adding viscosity increasing agents is contrary to the teachings of Keith. Only hindsight reconstruction would provide the necessary suggestion or motivation to modify pH and buffer conditions for the Kieth, and this would contravene the teachings of Kieth regarding viscosity of a scopolamine formulation. Finally, Keith and Joshi, even combined as proposed by Examiner, fail to encompass the claimed specific pH ranges and values, and the specific buffers and buffer concentrations, and there is no evidence of record providing specific motivation or guidance to "optimize" the Kieth formulation using such specific pH ranges/values.

Joshi is directed to "reversibly gelling aqueous compositions", and does not disclose the compositions of the claimed invention. As noted above, the disclosure of Kieth alone or combined with Joshi fails to teach or suggest the employment of PVA or any other gelling agents in an intranasal scopolamine formulation. Further with respect to desired pH values, Joshi neither suggests nor provides practical motivation to optimize the intranasal scopolamine formulation of Kieth by employing gelling agents, pH adjustment, or buffer selection strategies.

Moreover, even if pH adjustment to optimize gelling performance was a valid secondary teaching of Joshi, the claimed pH ranges would not be within the scope of such teachings. The Office cites Joshi for allegedly teaching that "compositions or formulations therein exhibit steady state flow characteristics at or near room temperature at a pH range of 2.5 to 6.5, i.e., a pH of between 3.0 and 5.0" (emphasis supplied by Examiner). The prior are teaches the much broader pH range of 2.5-6.5 , and that for only certain reversibly gelling agents (e.g., methylcellulose) is the narrower range of pH 3.0-5.0 proposed. Moreover, Joshi's teaching with respect to pH and its role in viscosity regulation are ambiguous. For example, while a stable methylcellulose formulation was reportedly prepared at the noted pH range of "between 3.0 and 5.0" (col. 7, lines 53-59), Joshi also teaches that "because methylcellulose is non-ionic, in solution alone it is visco-elastically stable over a wide range of pH from approximately 3 to 11." (col. 8, lines 47-49). Joshi describes generally all gel formulations and all active ingredients

between pH 3-11. Joshi fails to specifically point to a claimed pH range for a scopolamine/PVA formulation, below about 4.0, or about 3.5.

Applicants's specification expressly emphasizes the unique claimed pH value range for nasal scopolamine/PVA formulations, recited in the claims as below about pH 4.0 or about 3.5. This range departs substantially from a basic pH of greater than 7.6, which would be a preferred pH according to Joshi. The specified pH value range of Applicants' formulations unexpectedly yields an intranasal scopolamine formulation having the desired bioavailability and efficacy for treating motion sickness. Joshi does nothing to cure the deficiencies of Keith; rather, Joshi largely complicates and demonstrates the unpredictability of the effect of pH on the properties of an intranasal scopolamine formulation as claimed.

Moreover, Applicants' combination of features, including selection of PVA as a carrier for scopolamine in a formulation having a pH below about 4.0 or about 3.5, provides unexpected results over the art of record. In particular, it was widely known in the art that PVA should be used in a pH range of about 5-8. the *Handbook* page 383, paragraph 9, under that the indicated pH for polyvinyl alcohol is between 5.0 and 8.0. The reference cautions that "[p]olyvinyl alcohol decomposes in strong acids and softens or dissolves in weak acids or alkalis."

This express disclosure of the *Handbook*, teaching a pH range for polyvinyl alcohol well outside of Applicants' claimed pH range, teaches directly away from the instantly claimed formulations. By selecting a mildly acidic pH of 4.0 for an aqueous intranasal scopolamine formulation, as described and claimed by Applicants, one skilled in the art would have been directly led away from selecting PVA as a carrier based on the indicated range of pH compatibility of this emulsifier in the range of "between 5.0 and 8.0." These contradictory teachings likewise dispel any merit to the alleged teachings of Joshi which are only tangentially related to optimizing performance of reversibly gelling polymers by employing unspecified pH adjustments.

The Office further argues that Applicants make an "admission" in their specification regarding the prior art. In particular, the Office points to a general

statement in Applicants' disclosure that "many other excipients, known from the pharmaceutical literature, may be added to the formulations, such as preservatives, surfactants, co-solvents, adhesives, antioxidants, buffers, viscosity enhancing agents and agents to adjust the pH or the osmolarity" (emphasis supplied by Examiner). This statement does not amount to an admission that any particular additive or excipient previously known in the art would be an obvious modification to include in Applicants' intranasal scopolamine formulations. On the contrary, the Office's reliance on this general statement in Applicants' own disclosure once again evinces impermissible reliance on hindsight. Moreover, even if the subject statement were provided in a prior published reference, the general nature of the statement, lacking any specific reagents, ranges, or concentrations, would not rectify the deficiencies of the primary Kieth reference, so its value to bolster the rejection is nil.

The Office finally relies upon Joshi for allegedly disclosing that "the most promising drugs for incorporating into the aqueous drug delivery compositions therein include scopolamine (see col. 11 lines 32-33)." This construction of the Joshi reference is respectfully submitted to be improper. As an initial point, it would appear from the Office's statement that Joshi is now being characterized as a primary reference. That is to say, the Office proposes "incorporating" scopolamine "into the aqueous drug delivery compositions" of Joshi. This appears to be a back door attempt to draw in the teachings of Joshi by its reference to a laundry list of compounds that could be employed in a reversibly gelling delivery system. However, the Office's original purpose for citing Joshi et al. was to impart secondary teachings regarding pH to allegedly suggest modifications to the primary formulation of Kieth. Yet, as noted above, Kieth has nothing to do with reversibly gelling formulations--and in fact teaches directly away from viscosity increasing additives of any kind (see above).

Thus, the teachings of Joshi pertaining to selection of active agents for incorporation into reversibly gelling delivery systems are not properly integrated into a *Graham* obviousness analysis. Moreover, the Joshi reference lists 17 distinct classes of drugs and other agents that could be formulated in a reversibly gelling delivery system (col.s 11-12), among which scopolamine is but one of 12 "mydriatics" proposed for use

in "the treatment of eye conditions or diseases" (col. 11, lines 26-32). There is no actual disclosure of useful or effective scopolamine composition provided in this reference, and in fact the laundry list relates to "exemplary drugs and diagnostic agents" (col. 11, lines 1-2), and makes no mention of scopolamine as allegedly among "the most promising drugs for incorporating into the aqueous drug delivery compositions therein" as alleged by Examiner.

In view of the foregoing, the deficiencies of Keith are not remedied by the disclosures of five cited secondary references as advocated by the Office. There is no teaching or suggestion in these combined references to modify the simple, aqueous/alcohol scopolamine nasal spray formulation of Kieth characterized by Examiner as highly successful, if not optimal, to achieve any of the claimed novel aspects of Applicants' invention--for the reasons stated above and elsewhere presented in the record.

Concerning other, more specific aspects of the invention disclosed in the application and/or presented in the claims (e.g., use or selection of preservatives), these aspects are likewise respectfully submitted to be patentable in view of the foregoing, based in part on patentability of the independent claims as discussed above, and for additional reasons of record or unstated but evinced by Applicants' disclosure.

Based on the evidence and arguments presented herein above, Applicants respectfully submit that the stated grounds for rejection of claims 23-28 under 35 U.S.C. § 103(a) fail to establish a *prima facie* case of obviousness with respect to pending claims 29-50. Alternatively, if such *prima facie* case is deemed satisfied by the Office with regard to the pending claims, the evidence of record establishes that Applicants' formulations and methods yield "unexpected results" (e.g., in terms of utility, efficacy, compatibility, bioavailability, etc.)--sufficient to overcome such *prima facie* showing and evince nonobviousness of the claimed invention over the art of record. As explained by the Federal Circuit in In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995):

> One way for a patent applicant to rebut a prima facie case of unobviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.
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> [T]hat which would have been surprising to a person of ordinary skill in the art would not have been obvious. The principle applies most often to less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

Applicants' novel formulations clearly provide "unexpected results" over the art of record. The instantly-claimed scopolamine/PVA formulations are not only more stable than scopolamine formulations that use alternative carriers and gelling agents (e.g., methyl cellulose), but they also provide surprisingly enhanced bioavailability. Neither of these advantageous features is predicted by the combined teachings of Kieth and the cited secondary references-- for the reasons stated above. Moreover, Kieth teaches directly away from employing PVA for these purposes--based in part on the known activity of PVA to increase viscosity and the express teachings by Kieth to use a viscosity lowering agent (alcohol) in intranasal scopolamine formulations.

CONCLUSION

Accordingly, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425-455-5575.

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Respectfully submitted,

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